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10/076,632	02/19/2002	Paul Habermann	P 30,612 USA	2603

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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
12/12/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/076,632	HABERMANN, PAUL	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2006 and 07 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-14,21-28 and 30-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-14,21-28 and 30-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1, 7-14, 21-28, and 30-35 are pending in the application.

[2] Applicant's amendments to the claims, filed on 6/19/06 and 1/7/08, are acknowledged. The claim listing filed on 1/7/08 replaces all prior versions and listings of the claims.

[3] Receipt of a substitute sequence listing in computer readable form (CRF), a paper copy thereof, a statement of their sameness, and a statement that no new matter has been added to the specification by the paper copy of the sequence CRF, all filed on 12/27/06, is acknowledged.

[4] Applicant's arguments filed on 6/19/06 in response to the Office action mailed on 2/17/06 have been fully considered and are deemed to be persuasive to overcome at least one of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Sequence Compliance

[6] In order to fully comply with the requirements for a sequence listing, applicant is required to submit an amendment to the specification directing entry of the substitute sequence listing paper copy into the application. See box 2 under "Applicant Must

Provide" in the "Notice to Comply" attached to the Office communication mailed on 10/23/06.

Specification/Informalities

[7] Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/270,591, fails to provide adequate support in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The specification of the '591 provisional application, which is published in the German language, does not appear to provide descriptive support for at least the limitations of "a hirudin derivative which is at least about 80% homologous thereto" and "mini-proinsulin or a derivative thereof which is at least about 90% homologous thereto".

[8] The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: amendment to the specification to provide antecedent basis for claim 1 limitations defining "Hir" and "protein(Y)", particularly with respect to the limitations of “a hirudin derivative which is at least about 80% homologous thereto” and “mini-proinsulin or a derivative thereof which is at least about 90% homologous thereto” and claim 33 limitation “T is the 3’ segment of the sequence coding for bovine interleukin 2 which remains after cleavage thereof with NcoI restriction enzyme”. See the new matter rejection under 35 U.S.C. 112, first paragraph, below for additional explanation.

Claim Objections

[9] Claims 21, 26, and 28 are objected to in the recitation of "comprising further the step" and in order to maintain consistency of claim terminology, it is suggested that the noted phrase be amended to recite "further comprising the step”.

[10] Claim 30 is objected to in the recitation of “insulin” and in order to improve claim form, it suggested that “insulin” be replaced with “mini-proinsulin”.

[11] Claims 31-35 are objected to as being dependent upon canceled claim 2. In the interest of advancing prosecution, the examiner has interpreted claims 31-33 as being dependent from claim 1. Appropriate correction is required.

[12] Claims 34 and 35 are objected to in the recitation of “wherein protein(Y) is mini-proinsulin” and “wherein Hir is lepirudin”, respectively, and in order to substantially

improve claim form, it is suggested that the noted phrases be amended to recite "wherein protein(Y) is a nucleic acid sequence encoding mini-proinsulin" and "wherein Hir is a nucleic acid sequence encoding lepirudin", respectively.

Claim Rejections - 35 USC § 112, Second Paragraph

[13] Claims 1, 7-14, 21-28, and 30-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 1 (claims 7-14, 21-28, and 30-34 dependent therefrom) are indefinite in the recitation of "a nucleic acid sequence coding for hirudin…which is at least about 80% homologous thereto" and "a nucleic acid sequence encoding mini-proinsulin…which is at least about 90% homologous thereto" because it is unclear as to whether "thereto" refers to the nucleic acid sequence or to the amino acid sequence of hirudin or mini-proinsulin. For example, because of the degeneracy of the genetic code, a nucleotide difference between nucleic acid sequences may or may not alter the encoded amino acid. However, this is not the case with an amino acid difference between two polypeptides.

Also, it is noted that because a skilled artisan would not recognize the scope of those polypeptides considered to be "at least about" 80% homologous to hirudin or "at least about 90% homologous to mini-proinsulin" for reasons that follow. First, it is noted that the specification, prosecution history, and prior art fail to provide guidance regarding "at least about" with respect to the lower range of applicant's intended

percentage homology. Second, because there is no reference sequence, *e.g.,* a sequence identifier, and because the terms “hirudin” and “mini-proinsulin” do not refer to a specific sequence, there is no way to determine whether the sequences fall or do not fall within the recited percent homology. Consequently, it is unclear as to the scope of recited nucleic acids. It is suggested that applicant clarify the meaning of the claim, particularly with respect to the noted phrases.

Claim 35 has not been included because the claim is limited to protein(Y) being mini-proinsulin and Hir being lepirudin.

[b] Claim 33 (claims 34-35 dependent therefrom) is indefinite in the recitation of “T is the 3’ segment of the sequence coding for bovine interleukin 2 which remains after cleavage thereof with NcoI restriction enzyme”. Based on the wording of the limitation, it appears that coding sequence, *i.e.,* sequence that encodes a polypeptide, remains after NcoI cleavage. However, according to the specification at p. 11, “…the bovine interleukin 2 cDNA sequence which was connected via a KpnI restriction enzyme site and which contained, an NcoI restriction enzyme recognition site in the untranslated 3’ end and removed by KpnI/NcoI cleavage”, thus indicating the remaining sequence is 3’ untranslated sequence, not "sequence coding for” a protein as recited in the claim. Also, because it is unclear as to *the* specific sequence that was cleaved, a skilled artisan would not be able to determine the sequence remaining after NcoI cleavage. It is suggested that applicant clarify the meaning of the noted phrase.

Claim Rejections - 35 USC § 112, First Paragraph

[14] Claims 1, 7-14, 21-28, and 30-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

MPEP § 2163.II.A.3.(b) states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description". According to MPEP § 2163.I.B, "While there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure" and "The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc.*, 935 F.2d at 1563-64, 19 USPQ2d at 1117".

Claim 1 (claims 7-14, 21-28, and 30-35 dependent therefrom) recites the limitations "hirudin or a hirudin derivative which is at least about 80% homologous thereto" and "mini-proinsulin or a derivative thereof which is at least about 90% homologous thereto". Applicant points to paragraphs [005] and [006] and original claim 2 as showing descriptive support for the noted limitation. The examiner has reviewed

the cited support and it appears that applicant is relying on the disclosure at p. 4, bottom as providing descriptive support for the noted limitation.

This disclosure fails to provide adequate support because the recitation of "thereto" can be interpreted as encompassing homology to either nucleic acid or hirudin/mini-proinsulin, while the noted disclosure appears to only discuss homology to a protein. This disclosure further fails to provide adequate support for the limitation "hirudin or a hirudin derivative which is at least about 80% homologous thereto" because the noted disclosure teaches that a hirudin derivative can be at least about 80% homologous to a *natural hirudin isoform.* Claim 1 is not limited to a hirudin derivative that is at least about 80% homologous to a *natural hirudin isoform*. Instead, the claim recites "at least about 80% homologous thereto" – referring either to a nucleic acid encoding a hirudin or to the hirudin polypeptide and based on the disclosure of the specification, it appears the term "hirudin" is intended as encompassing both naturally occurring and non-naturally occurring hirudin polypeptides (*e.g.,* pp. 9-10, paragraph [032] and p. 11, paragraph 36). As such, the noted limitation is viewed as being broader than the cited descriptive support.

Claim 33 recites the limitation "T is the 3' segment of the sequence coding for bovine interleukin 2 which remains after cleavage thereof with NcoI restriction enzyme". In the response filed on 5/31/05, applicant points to Examples 1 and 2 of the specification (pp. 11-15). The examiner has reviewed the cited support. Apparently, applicant is relying on the disclosure at p. 11, middle, which discloses, "…the bovine interleukin 2 cDNA sequence which was connected via a KpnI restriction enzyme site

and which contained, an NcoI restriction enzyme recognition site in the untranslated 3' end...the cDNA sequence was readily removable from the plasmid via KpnI/NcoI cleavage". However, it is noted that the claim is not limited to bovine interleukin 2 cDNA sequence which was connected via a KpnI restriction enzyme site and which contained, an NcoI restriction enzyme recognition site in the untranslated 3' end and removed by KpnI/NcoI cleavage. Instead, the claim recites "3' segment of the sequence coding for bovine interleukin 2 which remains after cleavage thereof with NcoI restriction enzyme", which is a broader limitation than that supported by the disclosure because, for example, the sequence "coding" for bovine interleukin 2 can be genomic sequence, not cDNA.

Applicant is invited to show support for the limitations at issue.

[15] The written description rejection of claim(s) 1, 7-14, 21-28, and 30-33 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's amendment to the claims to require a structural relationship, *i.e.,* "at least about 80% homologous" and "at least about 90% homologous" between the "derivatives" and hirudin or mini-proinsulin, respectively.

[16] The scope of enablement rejection of claims 1, 7-14, 21-28, and 30-33 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a previous Office action. See paragraph 13 beginning at p. 9 of the 2/17/06 Office action. Claim 34 has been included in the

instant rejection as being dependent from claim 33. While limiting protein(Y) to being mini-proinsulin, claim 34 still encompasses derivatives of hirudin as recited in claim 1. Thus, claims 1, 7-14, 21-28, and 30-34 are rejected. Claim 35 has not been included because the claim is limited to protein(Y) being mini-proinsulin and Hir being lepirudin.

RESPONSE TO ARGUMENT: Beginning at p. 12 of the remarks filed on 6/19/06, applicant argues the claims specifically define a nucleic acid encoding a fusion protein comprising hirudin and mini-proinsulin and that given the state of the art and the disclosed guidance and direction, one skilled in the art can make the claimed invention without requiring undue experimentation.

Applicant's argument is not found persuasive. Contrary to applicant's position, the claims are not limited to encoding a fusion protein comprising hirudin and mini-proinsulin. Instead, the claims encompass "derivatives" of hirudin and mini-proinsulin that are not required to maintain the biological activity or activities of hirudin and mini-proinsulin. According to the specification at p. 3, paragraph [004] and remarks filed on 6/19/06 at p. 12, the use of hirudin in the fusion protein is as a transport/export moiety for improved recombinant protein production in a yeast. However, the specification fails to provide any guidance or direction for using those nucleic acids encoding fusion proteins that do not maintain the desired activity/utility of the working example fusion proteins. The effect(s) of amino acid modification is highly unpredictable and because the specification fails to provide any guidance regarding those "derivatives" of hirudin or mini-proinsulin that are likely to maintain and/or those that are not likely to maintain the desired activity/utility, a skilled artisan would have no expectation that "derivatives" of

hirudin or mini-insulin as encompassed by the claims would maintain their respective desired biological activity. Here, the specification fails to disclose a correlation between the amino acids and/or regions of hirudin protein to the function of increasing transport/export of a fusion protein from a yeast. Consequently, a skilled artisan would be required to practice undue experimentation to make and use the full scope of claimed nucleic acids.

Claim Rejections - 35 USC § 102

[17] The rejection of claim(s) 1, 7-14, 21, and 25-28 under 35 U.S.C. 102(b) as being anticipated by Dawson et al. is withdrawn. Although applicant's argument asserting the number of codons between the signal sequence and Hir is unpersuasive, the rejection is withdrawn in view of the claim amendment to limit protein(Y) as the examiner can find no teaching or suggestion in the prior art for a nucleic acid encoding a fusion of Hirudin with mini-proinsulin or derivatives thereof as encompassed by the claims.

Claim Rejections - 35 USC § 103

[18] The rejection of Claims 22 and 24 under 35 U.S.C. 103(a) as being unpatentable over Dawson et al. in view of Badziong et al. and the rejection of claim 23 under 35 U.S.C. 103(a) as being unpatentable over Dawson et al. in view of Badziong et al. as applied to claims 22 and 24 above and further in view of Mead et al. are withdrawn because, as noted above, the examiner can find no teaching or suggestion in the prior

art for a nucleic acid encoding a fusion of Hirudin with mini-proinsulin or derivatives thereof as encompassed by the claims

Claim Rejections – Double Patenting

[19] Claims 1 and 7-13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 6-12, and 27-37 of co-pending application 10/076,631 ("'631 application"). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '631 application anticipate the claims of this application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

[20] Claims 1, 9, 12-14, 21, and 25-28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-5, 8, and 10-18 of US Patent 7,202,059 (the '059 patent) in view of Dörschug et al. (US Patent 6,875,589) and Schmid et al. (US Patent 5,919,895). An obviousness-type

double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. The difference between the claims is that: 1) the claims of this application require protein(Y) to be mini-proinsulin, where "Y" of the '059 patent is recited as being pro-insulin or insulin and 2) the claims of this application require a Lys or Arg codon (moiety Z) before Hir, which is not required in the claims of the '059 patent. However, these are obvious variations because Dörschug teaches mini-proinsulin is a form of pro-insulin with a shortened B or C chain and is easily converted to insulin (column 1, lines 8-34) and Schmid teaches the advantage of placing an Arg at the N-terminus of a recombinantly expressed hirudin allows for removal of a fused signal sequence with trypsin (column 2, line 66 to column 3, line 1). Therefore, it would have been obvious for the nucleic acid of the ‘059 patent to encode Arg at the N-terminus of Hir and for "Y" to be mini-proinsulin. One would have been motivated to make such a modification in order to allow cleavage of the hirudin moiety from the signal sequence and because mini-proinsulin is an art-recognized form of proinsulin as per the teachings of Dörschug and Schmid.

RESPONSE TO ARGUMENT: At p. 15 of the remarks filed on 6/19/06, applicant argues the rejections are merely provisional as no patent has been issued. However, this is not found persuasive because at least one of the applications, *i.e.,* 10/076,634, has issued as US Patent 7,202,059 and the rejection is no longer provisional.

Conclusion

[21] Status of the claims:

- Claims 1, 7-14, 21-28, and 30-35 are pending.
- Claims 1, 7-14, 21-28, and 30-35 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656